Original Article

Efficacy of ALK inhibitors in Asian patients with ALK inhibitor-naïve advanced *ALK*-positive non-small cell lung cancer: a systematic review and network meta-analysis

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Background: A previous network meta-analysis (NMA) compared the efficacy of anaplastic lymphoma kinase (ALK) inhibitors in *ALK*-positive non-small cell lung cancer (NSCLC). The phase III INSPIRE study of iruplinalkib was published recently. The present study aimed to add the results related to iruplinalkib to the NMA.

Methods: A systematic literature search was performed in PubMed, Embase, Cochrane Library, Google, and Baidu. Randomized controlled trials (RCTs) reporting the independent review committee-assessed progression-free survival (PFS), objective response rate (ORR), or disease control rate (DCR) results of Asian patients with ALK inhibitor-naïve advanced *ALK*-positive NSCLC were eligible for inclusion in the NMA. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Bayesian fixed-effect models were used for the direct and indirect pairwise comparisons. This study was registered with PROSPERO (CRD42024555299).

Results: Eight studies, involving 1,477 Asian patients and seven treatments (crizotinib, alectinib, brigatinib, ensartinib, envonalkib, iruplinalkib, and lorlatinib), were included in the NMA. In terms of the overall risks of bias, all of the studies had "some concerns". All the next-generation ALK inhibitors were statistically superior to crizotinib in terms of PFS. Iruplinalkib had the best surface under the cumulative ranking curve (74.0%), followed by brigatinib (69.1%) and ensartinib (63.7%). Most of the pairwise comparisons did not reveal significant differences in the ORR and DCR. In terms of both the ORR and DCR, alectinib ranked first, followed by lorlatinib.

Conclusions: Next-generation ALK inhibitors had better efficacy than crizotinib in the treatment of Asian patients with ALK inhibitor-naïve advanced *ALK*-positive NSCLC. Iruplinalkib may have more favorable PFS benefit than other ALK inhibitors for Asians.

Keywords: Non-small cell lung cancer (NSCLC); anaplastic lymphoma kinase (ALK); targeted therapy; network meta-analysis (NMA)

Introduction

Lung cancer is the most incident tumor, with the highest cancer mortality rate worldwide (1). Anaplastic lymphoma kinase (*ALK*) alterations are a group of driver genes. Of which, *EML4-ALK* is the most frequent alteration, with incidence rates ranging from 3% to 7% in global patients with non-small cell lung cancer (NSCLC) (2-4). In Asians, approximately 9% of NSCLC patients have been reported to have the *ALK*-positive disease (5,6).

ALK tyrosine kinase inhibitors (TKIs) are recommended for the treatment of advanced *ALK*-positive NSCLC (7,8). Crizotinib, a first-generation ALK TKI, has been shown to have better efficacy than chemotherapy (9,10). In randomized controlled trials (RCTs), next-generation ALK TKIs (alectinib, brigatinib, ensartinib, envonalkib, iruplinalkib, and lorlatinib) result in longer progression-free survivals (PFSs) than crizotinib in patients with ALK TKI-naïve advanced *ALK*-positive NSCLC (11-21). However, no head-to-head RCTs have been conducted to examine different next-generation ALK TKIs in the ALK TKI-naïve setting. A previous network meta-analysis (NMA) indicated that global and Asian patients may have distinct prognoses after ALK TKI treatment in the first-line (treatment-naïve) setting (22). Further, in terms of PFS, lorlatinib has been shown to have the best efficacy for global patients, followed by alectinib and brigatinib (22). While for Asian patients, it is indicated that alectinib has a greater PFS benefit than other ALK TKIs (22).

The results of the phase III INSPIRE study of iruplinalkib were recently published (19,20). The INSPIRE study was not included in the latest NMA. Therefore, we conducted a systematic review and NMA to compare the efficacy of iruplinalkib and other ALK TKIs for Asian patients with TKI-naïve advanced *ALK*-positive NSCLC. The protocol was registered in PROSPERO (CRD42024555299). We present this article in accordance with the PRISMA NMA reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-604/rc).

Methods

A systematic literature search was performed in PubMed, Embase, and Cochrane Library to retrieve articles or meeting abstracts published up to December 26, 2023. Search engines (i.e., Google and Baidu) were also used to find eligible studies. The key search terms included "non-small cell lung cancer", "randomized controlled trial", "crizotinib", "alectinib", "brigatinib", "ceritinib", "ensartinib", "envonalkib", "iruplinalkib", and "lorlatinib". The detailed search strategy is summarized in Table S1. Finally, the reference lists of the relevant articles were checked to identify additional reports.

Eligible criteria

Studies were included in the NMA if the following criteria were met: (I) related to articles or meeting abstracts of a RCT written in English; (II) compared ALK TKIs for TKI-naïve advanced *ALK*-positive NSCLC; and (III) reported independent review committee (IRC)-assessed PFS, objective response rate (ORR), or disease control rate (DCR) results for Asian patients. If the full text was not available, the article was not included in the analysis. Two reviewers (X.L. and Y.X.) independently reviewed the titles, abstracts, and full texts of the articles. Any disagreements as to whether an article met the inclusion criteria were resolved through discussion or consultation with a third reviewer (S.H.).

Data extraction and risk of bias assessment

The following data were independently extracted from the eligible reports by two reviewers (C.W. and Q.C.) using a standardized sheet: first author's name, publication year, study name, registration number, country or region, race, number of patients, age, sex, treatment line, regimen,

Highlight box

Key findings
- Next-generation anaplastic lymphoma kinase (ALK) inhibitors had better efficacy than crizotinib in the treatment of Asian patients with ALK inhibitor-naïve advanced *ALK*-positive non-small cell lung cancer (NSCLC). And iruplinalkib was likely to have more favorable PFS benefit in Asians.

What is known and what is new?
- Previous network meta-analysis (NMA) compared ALK inhibitors. However, data of iruplinalkib were not included in the NMA.
- The present NMA provided the results of comparisons of each ALK inhibitors in efficacy.

What is the implication, and what should change now?
- Iruplinalkib showed encouraging PFS benefit for Asian patients with ALK inhibitor-naïve advanced *ALK*-positive NSCLC, and OS data are awaited.
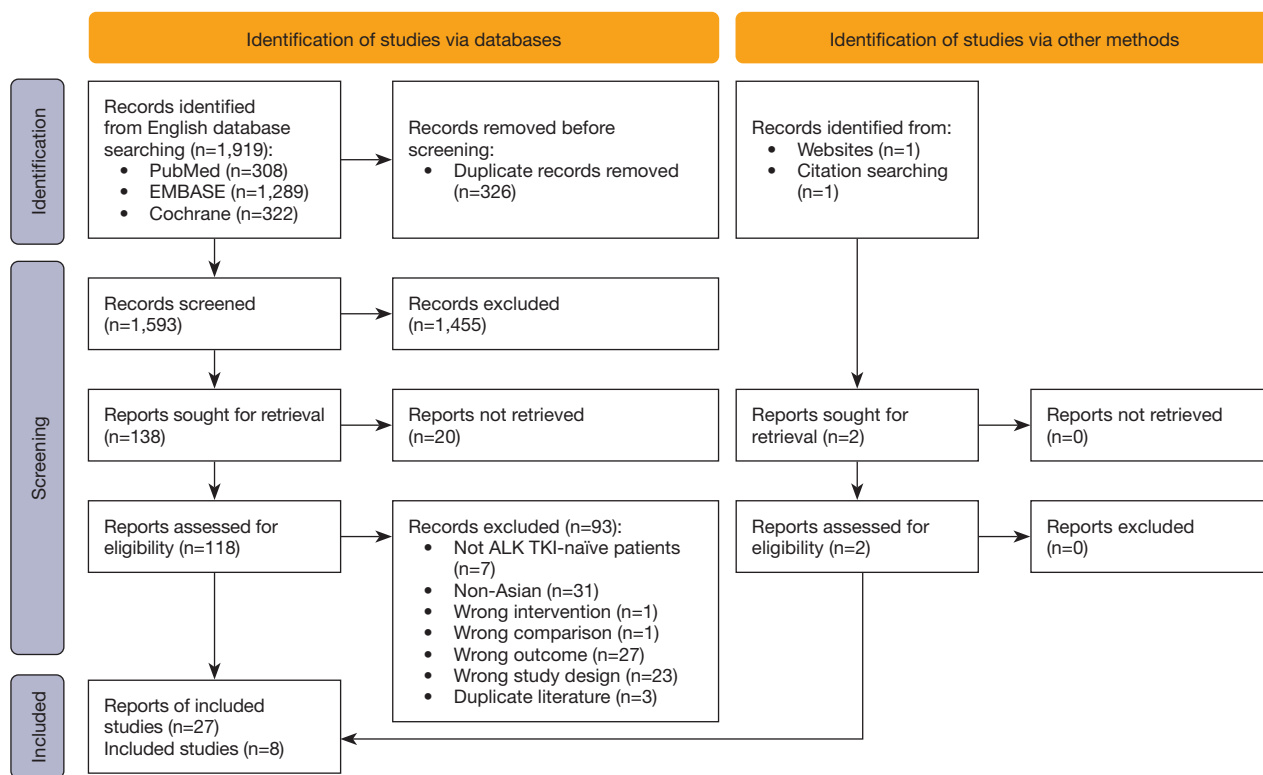
Figure 1 Flow chart of study selection. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

hazard ratio (HR) with confidence interval (CI) for IRC-assessed PFS between the experimental and control groups, and number of patients with an IRC-assessed objective response or disease control. If the results of a study had been reported multiple times, the latest efficacy results for Asian patients were included in the NMA, and the study characteristics were extracted from the latest report or another report at the discretion of the reviewers. If a report had results for global and Asian patients, only the data related to Asians were extracted. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool (23).

Statistical analysis

Bayesian fixed-effects models were used for the direct and indirect pairwise comparisons of the PFS, ORR, and DCR because most of the comparisons were made using only one study. The PFS results were expressed as the HR with the 95% credible interval (CrI). The ORR and DCR results were expressed as the odds ratio (OR) with the 95% CrI. Heterogeneity was not assessed because there were too few studies. As there was no closed loop of treatments,

neither local nor global inconsistency was evaluated. If a study only reported the CI of the HR for PFS other than the 95% CI, it was converted to the 95% CI using the Z-score. Cumulative ranking curves were plotted. Each curve represents a treatment. The horizontal axis represents the ranks. The vertical axis is the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. The surfaces under the cumulative ranking curve (SUCRAs) were also estimated. The SUCRA is a value between 0 and 100%. The higher the SUCRA, the more likely the drug is to be the best (24). The statistical analyses were conducted using the R packages "gemtc" and "rjags" of R software (version 4.3.0, R Core Team).

Results

Study selection and characteristics

In the initial search, 1,919 records were retrieved, and 326 duplicated records were removed. After the screening, 27 reports of eight studies, comprising a total of 1,477 Asian patients, were included in the analysis (*Figure 1*).

2018

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Table 1 Study characteristics

First author	Trial name/ number	Region	Experimental treatment	Control treatment	Sample size of Asians	No. of Asian patients who previously underwent chemotherapy for advanced disease	HR (95% CI) for PFS in Asians[†]	No. of Asian patients who achieved an objective response[†]	No. of Asian patients who achieved disease control[†]
Mok, 2017 (11)	ALEX	Global	Alectinib 600 mg bid	Crizotinib 250 mg bid	69/69	Not allowed	0.49 (0.30–0.79)	Not reported	Not reported
Nakagawa, 2020/ Hida, 2017 (12,13)	J-ALEX	Japan	Alectinib 300 mg bid		103/104	37/37	0.37 (0.26–0.52)	76 of 83/71 of 90[‡]	80 of 83/83 of 90[‡]
Zhou, 2019 (14)	ALESIA	Asia	Alectinib 600 mg bid		125/62	Not allowed	0.37 (0.22–0.61)	Not reported	Not reported
Ahn, 2022 (15)	ALTA-1L	Global	Brigatinib 180 mg qd with 7-day lead-in at 90 mg qd		59/49	19/12	0.35 (0.20–0.59)	47/35	53/45
Zhou, 2022/Horn, 2021 (16,17)	eXalt3	Global	Ensatinib 225 mg qd		77/84	15 of 73/21 of 78[§]	0.37 (0.23–0.58)	59 of 73/53 of 78[§]	66 of 73/70 of 78[§]
Yang, 2023 (18)	NCT04009317	China	Envonalkib 600 mg bid		131/133	33/32	0.47 (0.34–0.64)	107/94	120/118
Shi, 2023/Shi, 2024 (19,20)	INSPIRE	China	Iruplinalkib 180 mg qd with 7-day lead-in at 60 mg qd		143/149	24/25	0.34 (0.23–0.52)[¶]	133/133	138/142
Zhou, 2023 (21)	CROWN	Global	Lorlatinib 100 mg qd		59/61	Not allowed	0.40 (0.23–0.71)	46/35	53/52[ǀ]

[†], IRC-assessed results; [‡], based on patients with measurable lesions by an IRC; [§], based on modified intent-to-treat population; [¶], 98.02% CI; [ǀ], including one/ two patients with non-complete response or non-progressive disease. No., number; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; bid, twice a day; qd, once daily; IRC, independent review committee.

Four studies were international RCTs. One study was conducted in Asia, two studies in China, and one study in Japan. Treatments included crizotinib, alectinib, brigatinib, ensartinib, envonalkib, iruplinalkib, and lorlatinib. No eligible study of ceritinib was found. The characteristics of the selected studies are summarized in *Table 1*. All the studies had a "low risk" in terms of the missing outcome data but had "some concerns" in some of the other domains. In terms of the overall risks of bias, all of the studies had "some concerns" (Figure S1).

Efficacy

As Figure S2A shows, all the next-generation ALK TKIs were compared with crizotinib in terms of PFS, but there were no direct comparisons of the next-generation drugs. In terms of IRC-assessed PFS, the pairwise comparisons showed that the next-generation ALK TKIs (alectinib, brigatinib, ensartinib, envonalkib, iruplinalkib, and lorlatinib) had significantly better efficacy than crizotinib in Asians. However, no significant difference was found between each next-generation ALK TKI (*Figure 2*). In the ranking of IRC-assessed PFS, iruplinalkib had the highest SUCRA (74.0%). Thus, iruplinalkib was more likely to have the best efficacy of the drugs in Asians, followed by brigatinib, ensartinib, lorlatinib, and alectinib (SUCRAs: 69.1%, 63.7%, 54.8%, and 54.8%, respectively; *Figure 3*).

Six studies reported the ORR and DCR results (Figure S2B). The ORRs for alectinib, envonalkib, and lorlatinib were significantly better than the ORR for crizotinib. The ORs were 3.00 (95% CrI: 1.22–8.24), 1.86 (95% CrI: 1.04–3.39), and 2.68 (95% CrI: 1.22–6.09), respectively. No significant difference was found in the pairwise comparisons of the other treatments (*Figure 4*). The next-generation ALK TKIs (except brigatinib) had higher DCRs than crizotinib. None of the differences were statistically significant

Alectinib						
1.14 (0.63–2.07)	Brigatinib					
1.08 (0.64–1.82)	0.95 (0.46–1.93)	Ensartinib				
0.85 (0.57–1.26)	0.74 (0.40–1.39)	0.79 (0.45–1.38)	Envonalkib			
1.17 (0.73–1.89)	1.03 (0.52–2.02)	1.09 (0.59–2.01)	1.38 (0.82–2.32)	Iruplinalkib		
0.99 (0.54–1.84)	0.88 (0.40–1.91)	0.93 (0.45–1.91)	1.18 (0.62–2.24)	0.85 (0.42–1.71)	Lorlatinib	
0.40 (0.31–0.51)	**0.35 (0.20–0.60)**	**0.37 (0.23–0.59)**	**0.47 (0.34–0.65)**	**0.34 (0.23–0.51)**	**0.40 (0.23–0.70)**	Crizotinib

Figure 2 NMA of IRC-assessed PFS. The data are expressed as the HR (95% CrI). A HR less than 1 favors the column-defining intervention. The significant results are presented in bold. NMA, network meta-analysis; IRC, independent review committee; PFS, progressive-free survival; HR, hazard ratio; CrI, credible interval.
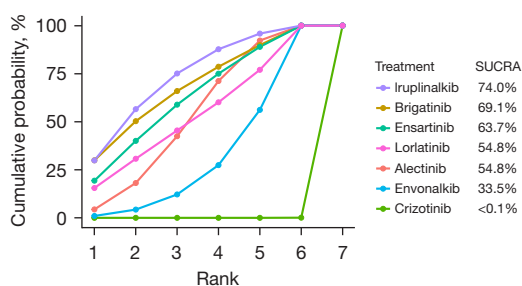

Figure 3 SUCRA of IRC-assessed PFS. SUCRA, surface under the cumulative ranking curve; IRC, independent review committee; PFS, progressive-free survival.

(*Figure 4*). The top three best treatments in terms of the ORR were alectinib, lorlatinib, and ensartinib (SUCRAs: 79.9%, 74.9%, and 56.3%, respectively; *Figure 5A*). In terms of the DCR, alectinib ranked first, followed by lorlatinib and envonalkib (SUCRAs: 78.4%, 61.8%, and 57.0%, respectively; *Figure 5B*).

Discussion

The present systematic review and NMA compared the efficacy of ALK TKIs for TKI-naïve advanced *ALK*-positive NSCLC in an Asian population. After a comprehensive literature search, eight RCTs were included in the NMA. The results indicated that next-generation ALK TKI resulted in longer PFSs than crizotinib. Iruplinalkib had the highest SUCRA. Thus, iruplinalkib may bring better PFS benefit than other ALK TKIs for Asian patients with TKI-naïve advanced *ALK*-positive NSCLC.

Several RCTs have shown that next-generation ALK TKIs are more efficacious than crizotinib. Thus, next-generation ALK TKIs have become the preferred treatment options for *ALK*-positive NSCLC (7,8). However, there is a lack of head-to-head comparisons between each next-generation ALK TKI. In the first-line setting, a previous NMA, for which the cut-off date was December 2022, found that lorlatinib had the best efficacy in terms of PFS for global *ALK*-positive NSCLC patients, followed by alectinib, brigatinib, and ensartinib. For Asian patients, the top three first-line treatments were alectinib, ensartinib, and brigatinib (22). The results of the phase III INSPIRE study of iruplinalkib were first presented at the World Conference of Lung Cancer in September 2023 (19). The full text of the study results was published in January 2024 (20). The HR for IRC-assessed PFS reached 0.34 (98.02% CI: 0.23–0.52), showing its promising anti-tumor activity. In the present study, the efficacy of iruplinalkib and other ALK TKIs were compared. Iruplinalkib resulted in the best PFS benefit, followed by brigatinib, ensartinib, lorlatinib, and alectinib. The rankings of these drugs differ to those reported in the previous NMA. There might be two reasons for this discrepancy. First, the restricted mean survival time model was used in the previous NMA, while the present NMA ranked treatments based on the SUCRA. Second, the previous study included RCTs comparing crizotinib and chemotherapy, and ceritinib and chemotherapy, which were excluded from the present NMA.

In terms of the ORR and DCR, we found that most of the pairwise comparisons did not show any statistically significant differences. This might be because the rates were quite high (ORR: approximately 70–90%; DCR: approximately 90%), and the sample sizes of Asians were too small to detect the minor differences. In the present study, in terms of both ORR and DCR, alectinib ranked first, followed by lorlatinib.

Alectinib	0.31 (0.04–2.19)	0.46 (0.07–2.62)	0.59 (0.10–2.92)	0.58 (0.08–3.66)	0.66 (0.10–4.00)	0.42 (0.09–1.63)
1.91 (0.54–7.22)	Brigatinib	1.44 (0.25–8.74)	1.87 (0.39–9.91)	1.86 (0.30–12.38)	2.09 (0.37–13.04)	1.32 (0.34–5.57)
1.50 (0.45–5.24)	0.79 (0.24–2.52)	Ensartinib	1.30 (0.33–5.17)	1.28 (0.25–6.69)	1.45 (0.30–7.22)	0.92 (0.30–2.75)
1.61 (0.55–5.08)	0.85 (0.29–2.48)	1.07 (0.42–2.86)	Envonalkib	0.99 (0.23–4.42)	1.12 (0.28–4.70)	0.71 (0.30–1.61)
1.85 (0.53–6.61)	0.97 (0.28–3.30)	1.23 (0.40–3.81)	1.14 (0.40–3.11)	Iruplinalkib	1.13 (0.21–5.93)	0.72 (0.20–2.33)
1.12 (0.33–4.04)	0.59 (0.17–1.97)	0.75 (0.25–2.25)	0.69 (0.25–1.86)	0.60 (0.19–1.97)	Lorlatinib	0.64 (0.20–1.92)
3.00 (1.22–8.24)	1.58 (0.65–3.88)	2.00 (0.96–4.39)	**1.86 (1.04–3.39)**	1.63 (0.72–3.87)	**2.68 (1.22–6.09)**	Crizotinib

Figure 4 NMA of the IRC-assessed ORR (lower left) and DCR (upper right). The data are expressed as the OR (95% CrI). An OR greater than 1 favors the column-defining intervention. The significant results are presented in bold. NMA, network meta-analysis; IRC, independent review committee; ORR, objective response rate; DCR, disease control rate; OR, odds ratio; CrI, credible interval.
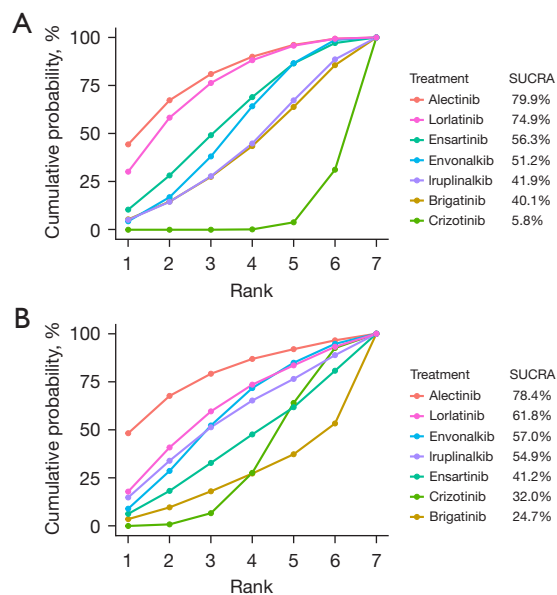

Figure 5 SUCRAs. (A) IRC-assessed ORR; (B) DCR. SUCRAs, surfaces under the cumulative ranking curve; IRC, independent review committee; ORR, objective response rate; DCR, disease control rate.

baseline characteristics, protocols, etc. across the studies. Thus, the results of the present NMA should be interpreted with caution.

Conclusions

Next-generation ALK TKIs showed significantly superior efficacy compared to crizotinib in the treatment of Asian patients with ALK TKI-naïve advanced *ALK*-positive NSCLC. Iruplinalkib may provide better PFS benefit than other TKIs for Asians.

Acknowledgments

Footnote

Due to insufficient data, overall survival (OS) was not analyzed in the present study. As surrogate endpoints, PFS is better correlated with OS, while ORR lacks validity for the surrogacy of OS (25). Thus, iruplinalkib, which results in the best PFS, may have better efficacy for Asians.

Our study had several limitations. First, the efficacy for the subgroups (e.g., patients with or without brain metastasis) and OS of Asians were not analyzed because the international RCT did not report these results (15,21). Additionally, transitivity, which is important for indirect comparisons, might be affected due to differences in the

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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